

Control of Respiratory Drive and Effort in Extracorporeal Membrane Oxygenation Patients Recovering from Severe Acute Respiratory Distress Syndrome

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ABSTRACT

Background: The amount of extracorporeal carbon dioxide removal may influence respiratory drive in acute respiratory distress syndrome (ARDS) patients undergoing extracorporeal membrane oxygenation (ECMO). The authors evaluated the effects of different levels of extracorporeal carbon dioxide removal in patients recovering from severe ARDS undergoing pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA).

Methods: The authors conducted a prospective, randomized, crossover study on eight spontaneously breathing ARDS patients undergoing venovenous ECMO since 28 ± 20 days. To modulate carbon dioxide extraction, ECMO gas flow (GF) was decreased from baseline resting protective conditions (*i.e.*, GF100%, set to obtain pressure generated in the first 100 ms of inspiration against an occluded airway less than 2 cm H₂O, respiratory rate less than or equal to 25 bpm, tidal volume less than 6 ml/kg, and peak airway pressure less than 25 cm H₂O) to GF50%-GF25%-GF0% during both PSV and NAVA (random order for ventilation mode). Continuous recordings of airway pressure and flow and esophageal pressure were obtained and analyzed during all study phases.

Results: At higher levels of extracorporeal carbon dioxide extraction, pressure generated in the first 100 ms of inspiration against an occluded airway decreased from 2.8 ± 2.7 cm H₂O (PSV, GF0%) and 3.0 ± 2.1 cm H₂O (NAVA, GF0%) to 0.9 ± 0.5 cm H₂O (PSV, GF100%) and 1.0 ± 0.8 cm H₂O (NAVA, GF100%; $P < 0.001$) and patients' inspiratory muscle pressure passed from 8.5 ± 6.3 and 6.5 ± 5.5 cm H₂O to 4.5 ± 3.1 and 4.2 ± 3.7 cm H₂O ($P < 0.001$). In time, decreased inspiratory drive and effort determined by higher carbon dioxide extraction led to reduction of tidal volume from 6.6 ± 0.9 and 7.5 ± 1.2 ml/kg to 4.9 ± 0.8 and 5.3 ± 1.3 ml/kg ($P < 0.001$) and of peak airway pressure from 21 ± 3 and 25 ± 4 cm H₂O to 21 ± 3 and 21 ± 5 cm H₂O ($P < 0.001$). Finally, transpulmonary pressure linearly decreased when the amount of carbon dioxide extracted by ECMO increased ($R^2 = 0.823$, $P < 0.001$).

Conclusions: In patients recovering from ARDS undergoing ECMO, the amount of carbon dioxide removed by the artificial lung may influence spontaneous breathing. The effects of carbon dioxide removal on spontaneous breathing during the earlier acute phases of ARDS remain to be elucidated. (*ANESTHESIOLOGY* 2016; 125:159-67)

PROTECTIVE mechanical ventilation (MV) with low tidal volume (V_t) and airway pressure is a life-saving treatment for patients with severe acute respiratory distress syndrome (ARDS).¹ However, severe ARDS patients, besides being deeply hypoxemic (requiring high positive end-expiratory pressure [PEEP]),² are characterized by increased dead space (requiring high minute ventilation)³ and low lung compliance.⁴ In these settings, coupling protective MV settings with acceptable blood gases may become difficult, and venovenous extracorporeal membrane oxygenation (ECMO) has been proposed to grant viable gas exchange while maintaining protective MV settings.⁵ Technologic improvements and the H1N1

What We Already Know about This Topic

- Extracorporeal membrane oxygenation permits lung rest in severe acute respiratory distress syndrome. However, spontaneous respiration during mechanical ventilation, especially with high respiratory drive, can worsen lung injury.

What This Article Tells Us That Is New

- Patients recovering from severe acute respiratory distress syndrome on extracorporeal membrane oxygenation while receiving ventilator support developed lower tidal volume and transpulmonary pressure when extracorporeal carbon dioxide extraction was increased and P_{aco₂} levels decreased. This suggests a mechanism for lessening lung injury in spontaneously breathing patients on extracorporeal membrane oxygenation.

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influenza outbreak recently boosted the clinical use of ECMO in adult patients.⁶ Upon the start of ECMO support, severe ARDS patients are usually deeply sedated and paralyzed to allow the application of controlled MV with low volume and pressure.^{7,8} After the first acute phase, and after sufficient improvement of the lung function, patients may be switched to some form of assisted MV rather than controlled MV while still on ECMO. Assisted MV is indeed claimed to improve the function of respiratory muscles, decrease risk of diaphragm dysfunction, reduce sedation needs, and favor weaning.⁹ Conversely, excessive inspiratory effort might aggravate lung injury.¹⁰ Previous studies showed that the amount of carbon dioxide removed extracorporeally might control spontaneous breathing.^{11,12} However, in acute severe ARDS patients, during the early phases of ECMO, respiratory drive appears often to be so high as to be rather independent from P_{aCO_2} and pH, while at a later stage of recovery assisted breathing can be applied with extracorporeal gas exchange still on.^{13,14}

In the current study, we tested the effects of changes in the amount of extracorporeal carbon dioxide removal upon the spontaneous breathing activity of a group of ARDS patients on ECMO and whose respiratory function had improved enough to achieve stable conditions under assisted ventilation. Moreover, to enhance clinical translation, we changed the amount of carbon dioxide extraction while patients were undergoing two different assisted ventilation modes. Indeed, optimal coupling of extracorporeal support and spontaneous ventilation should allow adequate exercise of respiratory muscles and grant protective ventilation while avoiding both muscle fatigue and overassistance. Recent data suggested that neurally adjusted ventilatory assist (NAVA) might be a promising assisted mode of MV in ECMO patients^{13,14}; a study by Karagiannidis *et al.*¹³ showed that NAVA could obtain autoregulation of protective ventilation during ECMO, while our group described improved patient-ventilator interaction during NAVA in comparison to pressure support ventilation (PSV).¹⁴ During NAVA, the support granted by the ventilator is proportional to the instantaneous value of the diaphragm electrical activity (EAdi),¹⁵ which is highly influenced by the extracorporeal support level.¹³ On the contrary, the level of ventilation assist during PSV is constant, even in the presence of changes in the inspiratory effort. In the current study, therefore, we also compared the effects of different levels of extracorporeal carbon dioxide removal during NAVA and PSV.

Materials and Methods

Severe ARDS patients undergoing assisted MV for at least 24 h while still on venovenous ECMO admitted from June 2013 to March 2014 to the intensive care unit of San Gerardo Hospital, Monza, Italy, were considered eligible for inclusion. All patients were on venovenous ECMO with femorofemoral access. Drainage and return of blood were facilitated using heparin-coated, spring wire-reinforced

cannulas of 21 to 28 Fr to allow a blood flow as high as 5 l/min. ECMO blood flow usually ranged between 2.5 and 3.5 l/min, while sweep gas flow (GF) was between 4 and 10 l/min to maintain adequate arterial oxygenation and normocapnia. Controlled MV with V_t less than or equal to 4 ml/kg was implemented from ECMO day 1 until there was sufficient recovery of respiratory function and clinical stability (*i.e.*, systolic blood pressure more than or equal to 90 mmHg with no vasoactive drugs and SpO_2 more than 90% with F_{IO_2} less than or equal to 60% and PEEP less than 15 cm H_2O).¹⁴ Then, neuromuscular blocking agents were discontinued; sedative drugs were titrated to Richmond agitation sedation scale values of -3 to -1, and a trial of assisted breathing (on PSV) was conducted. Exclusion criteria were age less than 18 yr, hemodynamic instability, contraindications to insert a NAVA-dedicated nasogastric tube, and refusal by the attending physician. The Ethical Committee of the San Gerardo Hospital, Monza, Italy, approved the study, and informed consent was obtained for each subject according to local regulations.

At enrolment, we collected data on age, sex, predicted body weight, Simplified Acute Physiology Score II values on intensive care unit admission, ARDS etiology, respiratory system compliance, arterial and mixed venous blood gases analyses, ventilation and ECMO settings (blood flow, sweep GF), and days on ECMO.

Throughout the whole study period, a calm environment was established to avoid stress and abrupt arousals. All patients were already connected to a mechanical ventilator that could deliver both PSV and NAVA (SERVO-i[®], Maquet, Sweden), which was set to PSV. Before the start of the study, ECMO sweep GF was regulated to obtain protective baseline conditions, defined as a pressure generated in the first 100 ms of inspiration against an occluded airway (P0.1) less than 2 cm H_2O and respiratory rate (RR) less than or equal to 25 bpm, with PSV level set to obtain $V_t = 3$ to 5 ml/kg with peak inspiratory pressure below 25 cm H_2O . PEEP, F_{IO_2} , ECMO blood flows, and sedation level were clinically set and left unchanged during the whole study.

A nasogastric tube with NAVA electrodes (Maquet) and an esophageal balloon (Cooper Surgical, USA) were positioned according to the manufacturer's instructions for the EAdi signal¹⁶ and to the standard calibration procedure of esophageal pressure (P_{es}) for spontaneously breathing patients.¹⁷ The NAVA catheter was connected to the ventilator, which was connected to a Personal Computer (PC₁) through its serial port. The PC₁, by means of dedicated software (Labview, National Instruments, USA), acquired waveforms of airway pressure, airflow, and EAdi from the ventilator and forwarded them as analog outputs (DAQcard; National Instruments) to another PC (PC₂). Contemporarily, two air-filled pressure transducers (T100209A, Edwards Lifesciences, USA) were connected to the airway opening and to the esophageal balloon, and their signals were acquired on PC₂ by a data acquisition system (PowerLab,

ADInstruments, USA). In this way, PC_2 continuously recorded during the whole study period at a sampling frequency of 100 Hz all the aforementioned waveforms (*i.e.*, airway pressure, flow, volume, EAdi, and Pes) for off-line analyses.^{18,19}

After 20 min, criteria for baseline conditions were checked again and the study protocol started. We modified ECMO GF to induce significant variations in the amount of carbon dioxide extracted; the study consisted of two crossover phases, randomized by computer-generated method for the ventilation mode (fig. 1):

- *PSV*: This phase consisted of four steps lasting 20 min each: patients were on PSV set as explained above, while ECMO GF was progressively decreased from resting baseline conditions to 50%-25%-0% of its value.
- *NAVA*: Patients were switched to NAVA with baseline resting ECMO GF and NAVA gain set to obtain peak pressure and V_t comparable to PSV. Then, the same four decremental levels of ECMO GF (resting baseline-50%-25%-0%) were applied.

The protocol was interrupted if the RR became more than 40 breaths/min and/or the heart rate more than 140 beats/min and/or the systolic blood pressure more than 180 mmHg and/or the patients developed diaphoresis or anxiety.

Right after the end of each GF step and immediately before the next, we collected ventilation settings, arterial and mixed venous blood gas analyses, hemodynamics, natural lung carbon dioxide production and membrane lung carbon dioxide production (V_{CO_2} -ML), the negative airway P0.1, and the ratio between airway pressure drop and the corresponding EAdi value during end-expiratory occlusion (*i.e.*, the muscle pressure [P_{muscle}]/EAdi [PEI] index, which indicates the pressure developed by the inspiratory muscles per each microvolt of EAdi).¹⁸ V_{CO_2} was calculated as the mean expired carbon dioxide concentration collected in a semioccluded chamber and measured through an infrared carbon dioxide analyzer (WMA-4 CO₂ Analyzer, PP Systems, USA) multiplied by the patients' minute ventilation (natural lung carbon dioxide production) or by ECMO GF (V_{CO_2} -ML).

Waveform data were analyzed off-line. The P_{muscle} waveform was then generated as the instant-by-instant difference between Pes and the chest wall elastic recoil curve (equal to the product of the volume by chest wall elastance, measured by occlusions during controlled ventilation at the end of the study). The transpulmonary pressure (P_T) waveform, instead, was calculated as the instant-by-instant difference between airway pressure and Pes. For each of the four PSV and NAVA steps, we averaged values from 10 to 20 breaths avoiding waveform sections of poor signal quality (*e.g.*, presence of

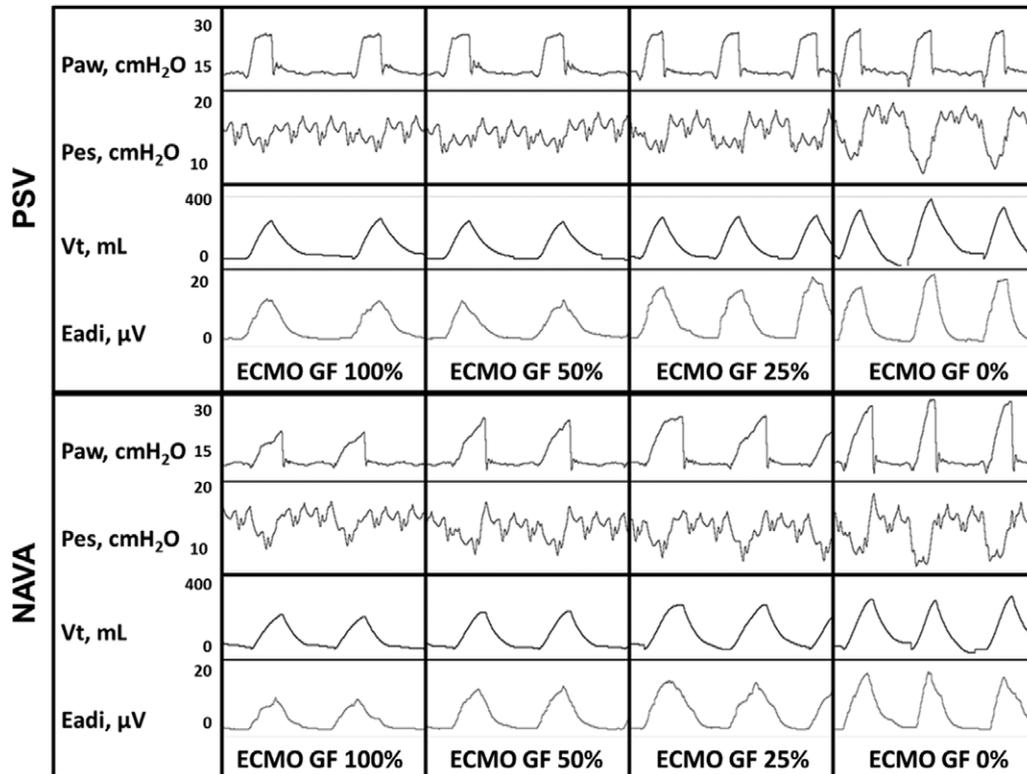


Fig. 1. Study protocol. Tracings of airway pressure (Paw), esophageal pressure (Pes), tidal volume (Vt), and diaphragm electrical activity (Eadi) from one representative study patient during pressure support ventilation (PSV) and neurally adjusted ventilatory assist (NAVA). Extracorporeal membrane oxygenation gas flow (ECMO GF) was modified from baseline resting conditions (ECMO GF100%) to 50% (ECMO GF50%), 25% (ECMO GF25%), and 0% (ECMO GF0%) to vary the amount of extracorporeal carbon dioxide removal (see text for details).

peristaltic waves on the Pes signal) to obtain the following variables:

- V_t
- RR
- Expired minute ventilation
- Peak airway pressure ($P_{aw_{peak}}$)
- Peak EAdi value
- Highest muscle pressure
- Highest transpulmonary pressure along inspiration (P_{L-max})
- Muscle pressure time product to assess patients' work of breathing

Statistical Analyses

Study sample size was similar to that in previous studies.^{13,14} Data are expressed as mean \pm SD. Two-way repeated measure ANOVA was used to assess differences and interactions between ventilator strategies (PSV *vs.* NAVA) and treatments (the four decreasing GF levels). The Holm-Sidak test *versus* a control group was used for *post hoc* comparisons with resting baseline GF and PSV phase as references. The coefficient of determination (R^2) was calculated by the Pearson correlation to assess significant association between variables. Statistical significance was defined as a $P < 0.05$. Statistical analyses were performed by SigmaPlot 11.0 (Systat Software Inc., USA).

Results

Patients' characteristics are summarized in table 1. We enrolled eight consecutive patients recovering from severe ARDS and undergoing ECMO for 28 ± 20 days, who had previously been on controlled MV for 25 ± 20 days. As expected, clinical application of assisted MV reflected a relative improvement in respiratory function; however, intrapulmonary shunt fractions were still 0.32 ± 0.13 and respiratory system compliance was 36 ± 14 ml/cm H_2O .

Baseline condition was characterized by ECMO GF of 3.2 ± 0.5 l/min, PSV level of 7 ± 2 cm H_2O , and NAVA gain of 1.1 ± 0.5 cm $H_2O/\mu V$ (tables 1 and 2): these settings granted similar protective V_t and $P_{aw_{peak}}$ values during both PSV and NAVA, with relatively low patients' drive and effort (*i.e.*, RR, $P_{0.1}$, P_{musc} , and peak EAdi values; Tables 2 and 3). The membrane lung carbon dioxide production (*i.e.*, V_{CO_2-ML}) during baseline resting condition ranged from around 30% to more than 75% of total patients' carbon dioxide production (table 2 and fig. 2A).

All patients uneventfully completed the study protocol. During both PSV and NAVA, decreasing the GF significantly decreased extracorporeal CO_2 removal while increasing patients' respiratory drive: indeed, patients' RR and $P_{0.1}$ increased (tables 2 and 3 and fig. 2B). Moreover, decreasing GF increased patient effort (*i.e.*, highest P_{musc} and pressure time product; fig. 2C) but to a more significant extent during PSV in comparison with NAVA (table 3). In fact, as we hypothesized and at variance from

Table 1. Characteristics of the Eight Spontaneously Breathing Patients Recovering from Severe Acute Respiratory Distress Syndrome Undergoing Extracorporeal Membrane Oxygenation Enrolled in the Study

Patient No.	Age (yr)	Sex	SAPS II	Severe ARDS Etiology	Days on ECMO before Enrollment	Days on Controlled MV before Enrollment	Tracheostomy at Enrollment	Cris (ml/cm H_2O)	Intrapulmonary Shunt	PEEP (cm H_2O)	PSV Level (cm H_2O)	NAVA Gain (cm $H_2O/\mu V$)	ECMO BF (l/min)	In-hospital Survival
1	56	M	53	Pneumonia	18	15	N	39	0.27	16	7	1.2	3.0	S
2	51	M	38	Trauma	57	53	Y	35	0.31	15	8	0.6	2.9	S
3	51	M	46	Pneumonia	13	12	Y	60	0.30	16	8	0.5	2.4	S
4	50	M	23	Acute interstitial pneumonitis	41	33	Y	22	0.57	8	9	1.2	3.7	NS
5	40	F	56	Pneumonia	15	10	Y	30	0.29	12	5	1.2	4.0	S
6	64	M	35	Pneumonia	22	20	Y	30	0.36	8	6	0.5	3.0	S
7	29	F	57	Pneumonia	6	4	N	51	0.40	15	6	1.5	2.9	S
8	40	F	32	Pneumonia	56	55	Y	18	0.10	12	10	2	3.0	S
Mean \pm SD	48 ± 11	5 M/3 F	42 ± 12	7 primary/1 extrapulmonary	28 ± 20	25 ± 20	6 Y/2 N	36 ± 14	0.32 ± 0.13	13 ± 3	7 ± 2	1.1 ± 0.5	3.2 ± 0.5	7 S/1 NS

ARDS = acute respiratory distress syndrome; BF = blood flow; Cris = respiratory system compliance; ECMO = extracorporeal membrane oxygenation; MV = mechanical ventilation; N = no; NAVA = neurally adjusted ventilatory assist; NS = nonsurvivor; PEEP = positive end-expiratory pressure; PSV = pressure support ventilation; S = survivor; SAPS II = simplified acute physiology score II; Y = yes.

Table 2. Variations in the Breathing Pattern and Gas Exchange during Decrease of Extracorporeal Membrane Oxygenation Support in Patients Recovering from Severe Acute Respiratory Distress Syndrome Undergoing Pressure Support and Neurally Adjusted Ventilatory Assist

Characteristic	Ventilation Mode	ECMO GF100% (Baseline)	GF50%	GF25%	GF0%	P Value		
						Ventilation Mode	GF	Interaction
ECMO GF (l/min)	PSV	4.4±1.2	2.2±0.6*	1.1±0.3*	0.0±0.0*	0.99	< 0.001	0.99
	NAVA	4.4±1.2	2.2±0.6*	1.1±0.3*	0.0±0.0*			
Total Vco ₂ (ml/min)	PSV	185±48	194±45	202±54	207±34	0.49	0.38	0.71
	NAVA	194±63	204±63	203±53	206±34			
Vco ₂ ML/total (%)	PSV	55±18	40±16*	24±10*	0±0*	0.84	< 0.001	0.55
	NAVA	56±20	38±16*	24±9*	0±0*			
RR (bpm)	PSV	17±4	19±5*	23±5*	27±6*	0.46	< 0.001	0.30
	NAVA	18±6	20±6	24±6*	27±5*			
MVe (l/min)	PSV	5.2±1.8	6.3±2.3*	8.5±2.3*	11.0±2.7*	0.01	< 0.001	0.47
	NAVA	6.2±2.9	7.8±3.0*†	10.1±3.4*†	12.5±3.1*†			
pH	PSV	7.43±0.04	7.42±0.05	7.41±0.04*	7.40±0.05*	0.09	0.001	0.54
	NAVA	7.43±0.05	7.42±0.03	7.42±0.05	7.41±0.04*			
Paco ₂ (mmHg)	PSV	43±4	45±3	46±4*	48±5*	0.08	< 0.001	0.58
	NAVA	43±4	44±4	45±4	46±4*			
Pao ₂ (mmHg)	PSV	89±12	95±12	114±24*	97±26	0.14	< 0.01	0.21
	NAVA	79±15	100±21*	103±21*	97±26*			

*P < 0.05 by Holm-Sidak *post hoc* test vs. gas flow (GF) 100%. †P < 0.05 by Holm-Sidak *post hoc* test vs. pressure support ventilation (PSV). ECMO = extracorporeal membrane oxygenation; ML = membrane lung; MVe = expired minute ventilation; NAVA = neurally adjusted ventilatory assist; RR = respiratory rate; VCO₂ = carbon dioxide production.

PSV, the ventilation assist delivered by NAVA increased when ECMO support decreased (table 3): this led to larger increase in minute ventilation, V_t, and P_{aw,peak} at lower

level of carbon dioxide removal during NAVA than during PSV (table 3 and fig. 3, A–C). During both PSV and NAVA, P_{L,max} was linearly correlated with the amount of

Table 3. Ventilation Variables during Decrease of Extracorporeal Membrane Oxygenation Support in Patients Recovering from Severe Acute Respiratory Distress Syndrome Undergoing Pressure Support and Neurally Adjusted Ventilatory Assist

Characteristic	Ventilation Mode	ECMO GF100% (Baseline)	GF50%	GF25%	GF0%	P Value		
						Ventilation Mode	GF	Interaction
Vt (ml/kg)	PSV	4.9±0.8	5.3±1.0	5.8±0.9*	6.6±0.9*	0.01	< 0.001	0.26
	NAVA	5.3±1.3	6.1±1.1*†	6.8±1.1*†	7.5±1.2*†			
Paw _{peak} (cm H ₂ O)	PSV	21±3	21±3	21±3	21±3	< 0.01	< 0.001	0.001
	NAVA	21±5	22±4*†	24±4*†	25±4*†			
EAdi _{peak} (μV)	PSV	6.3±3.8	8.3±5.6*	10.0±6.4*	12.1±6.6*	0.58	< 0.001	0.62
	NAVA	7.1±5.3	8.8±6.2*	10.3±6.7*	12.0±7.4*			
Ventilation support (cm H ₂ O)	PSV	6±2	7±2	7±2	8±2	< 0.01	< 0.001	0.25
	NAVA	7±1	8±1*†	9±2*†	10±2*†			
P _{L,max} (cm H ₂ O)	PSV	7±4	8±4	9±5*	10±5*	0.31	< 0.001	0.23
	NAVA	7±5	8±5	9±6*	10±7*			
P0.1 (cm H ₂ O)	PSV	0.9±0.5	1.6±1.2	2.4±1.8*	2.8±2.7*	0.91	< 0.001	0.81
	NAVA	1.0±0.8	1.6±1.0	2.3±1.5*	3.0±2.1*			
P _{musc,max} (cm H ₂ O)	PSV	4.5±3.1	5.5±4.0	6.6±4.8*	8.5±6.3*	0.04	< 0.001	0.03
	NAVA	4.2±3.7	4.6±3.8	5.2±4.3*†	6.5±5.5*†			
PTP (cm H ₂ O s)	PSV	1.2±1.1	1.9±2.3	2.5±2.6*	3.2±3.0*	0.06	< 0.001	0.98
	NAVA	2.3±2.8	2.7±3.0	3.4±3.6*	4.2±4.9*			
PEI (cm H ₂ O/μV)	PSV	1.3±1.7	1.2±1.0	1.8±1.4	1.8±1.2	0.23	0.15	0.46
	NAVA	1.2±1.3	1.0±0.7	1.4±1.2	1.4±1.2			

*P < 0.05 by Holm-Sidak *post hoc* test vs. gas flow (GF) 100%. †P < 0.05 by Holm-Sidak *post hoc* test vs. pressure support ventilation (PSV). EAdi_{peak} = maximal electrical activity of the diaphragm during inspiration; ECMO = extracorporeal membrane oxygenation; NAVA = neurally adjusted ventilatory assist; P0.1 = pressure generated in the first 100ms of inspiration against an occluded airway; Paw_{peak} = peak airway pressure; PEI = P_{musc}/EAdi index; P_{L,max} = maximal inspiratory transpulmonary pressure; P_{musc,max} = maximal inspiratory muscles pressure; PTP = pressure time product; Vt = tidal volume.

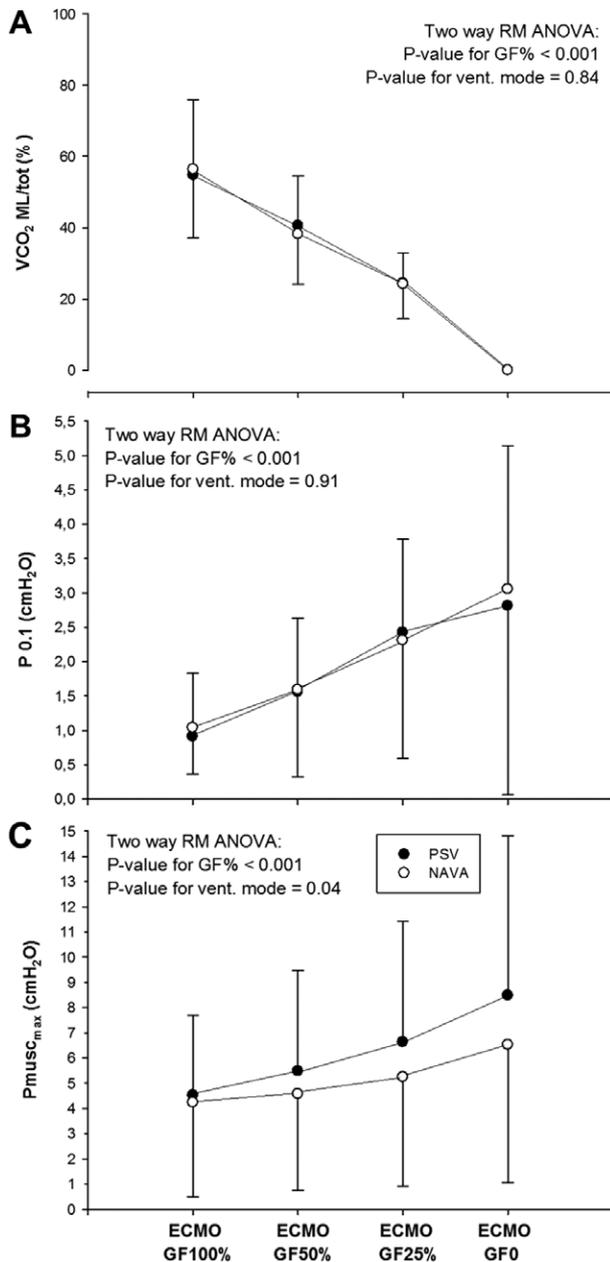


Fig. 2. Effects of extracorporeal membrane oxygenation (ECMO) support on respiratory drive and effort. Decreasing the amount of carbon dioxide extracted by ECMO (*i.e.*, the membrane lung carbon dioxide production [V_{CO_2}] ML:tot ratio; **A**) by modification of ECMO sweep gas flow (ECMO GF) led to significantly higher pressure generated in the first 100ms of inspiration against an occluded airway (P0.1; *i.e.*, a sign of respiratory drive; **B**) and maximal inspiratory muscles pressure (P_{musc_{max}}; *i.e.*, a measure of breathing effort; **C**) values. During neurally adjusted ventilatory assist (NAVA), the latter increased less than during pressure support ventilation (PSV) probably due to increased support by the ventilator (see text for details). Data are expressed as mean and SD. RM ANOVA = repeated measures ANOVA.

carbon dioxide extracted by ECMO (fig. 4) but, at lower GF values, P_{L-max} did not differ between the two ventilation modes (table 3).

Interestingly, P_{ao_2} increased when the GF was decreased during both NAVA and PSV (table 2).

Finally, the PEI index did not differ among any of the combinations of ECMO supports and ventilation modes tested (table 3).

Discussion

In spontaneously breathing patients recovering from severe ARDS and undergoing ECMO, the amount of carbon dioxide removed by the artificial lung critically impacts patients' respiratory drive, work of breathing, and ventilation volumes and pressures. Minute ventilation, V_t , and airway pressure increase to a lesser extent in response to decreased extracorporeal carbon dioxide removal during PSV than during NAVA. Finally, the PEI index value remains stable throughout different combinations of ECMO support and assisted ventilation mode.

In the current study, we confirmed that the amount of carbon dioxide removed by the membrane lung influences respiratory drive and effort in patients on ECMO, with sufficient recovery from severe ARDS as to tolerate assisted breathing. Previously, few animal studies showed that extracorporeal carbon dioxide removal could be so powerful to induce apnea in both healthy and injured models.^{20,21} Moreover, two studies showed similar findings in patients: a first seminal report by Marcolin *et al.*¹¹ showed that, in spontaneously breathing acute respiratory failure patients, increased ECMO GF critically influences minute ventilation; secondly, a more recent report by Karagiannidis *et al.*¹³ showed increased EAdi values by decreased ECMO GF. In this study, decreased extracorporeal carbon dioxide removal influenced the breathing pattern, so that patients increased RR and effort. In this way, two parallel and clinically relevant effects may be obtained: on the one hand, respiratory muscles activity is increased and disuse myopathy might be decreased,²² in addition to beneficial hemodynamic effects²³; on the other hand, all the critical determinants of ventilation-induced lung injury (VILI) like V_t ,¹ RR,²⁴ minute ventilation,²⁴ and airway and transpulmonary pressure^{25,26} may exceed the protective limits. Indeed, spontaneous breathing in ARDS showed both beneficial and detrimental effects, with studies suggesting deleterious effects in more severe ARDS stages.¹⁰ If this holds true, spontaneous breathing in ARDS patients undergoing ECMO might be hazardous when applied too early, while waiting for some clinical signs of relative improvements might be regarded as a wiser choice. Moreover, common clinical practice shows that implementation of spontaneous breathing in the early phases of severe ARDS is often impossible. However, due to the relatively late phase in which our patients were studied, our results might be regarded as only marginally relevant to understand the respiratory physiology of spontaneously breathing severe ARDS patients undergoing ECMO in the acute early phases.

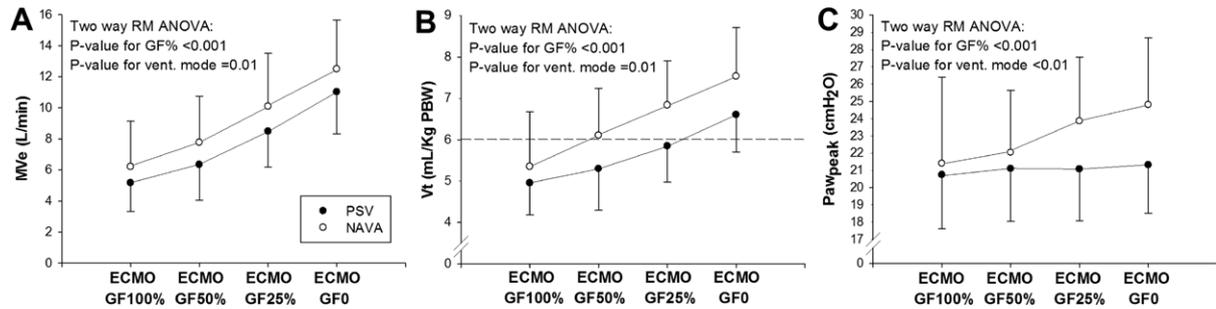


Fig. 3. Effects of extracorporeal membrane oxygenation (ECMO) support on ventilation volume and pressure. In the presence of reduced ECMO sweep gas flow (ECMO GF) and decreased extracorporeal carbon dioxide removal, we observed significant increase of expired minute ventilation (MVE; A), tidal volume (Vt; B), and peak airway pressure (Paw_{peak}; C). However, during neurally adjusted ventilatory assist (NAVA), all of these three variables increased more than during pressure support ventilation (PSV). Data are expressed as mean and SD. PBW = predicted body weight; RM ANOVA = repeated measures ANOVA.

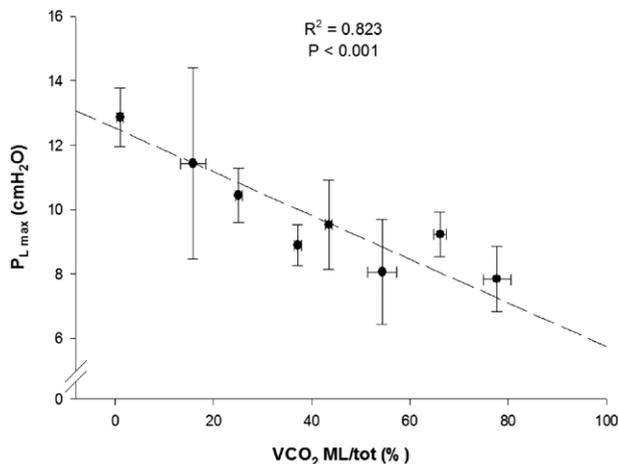


Fig. 4. Correlation between extracorporeal carbon dioxide removal and transpulmonary pressure. The maximal inspiratory transpulmonary pressure (P_{Lmax}) was linearly correlated with the amount of carbon dioxide removed by the extracorporeal membrane lung (ML) divided by total patient's carbon dioxide production (VCO₂ ML:tot). Data represent mean and standard error of each VCO₂ ML:tot octyl.

We also showed that, when the amount of carbon dioxide removed by ECMO is reduced, the increase in some key VILI determinants such as minute ventilation, Vt, and airway pressure²⁵ is less pronounced during PSV than during NAVA. During NAVA, indeed, the ventilation support is proportional to patient effort (*i.e.*, to the instantaneous EAdi value).¹⁴ On the contrary, during PSV, the inspiratory support provided by the ventilator is fixed and it does not change even in the presence of increased patient effort. However, the following concepts must be underlined: (1) NAVA gain (as well as pressure support level) can be modified during decreased ECMO support, and this might obtain more comparable results; (2) some relevant potential VILI factors did not differ during NAVA, such as P_{Lmax} (because Paw_{peak} augmented more during NAVA but δ Pes increased less because of increased support) and RR; and (3) during NAVA, the biologic breath-to-breath variability is usually preserved and patient-ventilator interaction is improved,¹³⁻¹⁵ and both

these factors might positively contribute to decrease the risk of VILI.

We showed that PEI value is stable throughout all the combinations of ECMO GFs and assisted MV modes studied. This result confirms our previous finding that PEI does not change when ventilation support varies.¹⁸ Thus, actual and previous results suggest the hypothesis that PEI might be regarded as an intrinsic physiologic characteristic of a patient, rather than being dependent on MV settings. If so, PEI value (or maybe evolution of PEI over time) might also possess clinical significance *per se*, for example, as an accurate indicator of the ability of the patient to succeed in spontaneous breathing trial and extubation.

In our patients, oxygenation improved when extracorporeal carbon dioxide removal decreased. This is probably due to increased diaphragm contraction and ventilation of dependent better-perfused lung regions²⁷ with improved ventilation/perfusion matching and/or to increased Vt and minute ventilation.

There are a few relevant limitations in this study: (1) Patients' sample size was limited, and our results, especially on the comparison between PSV and NAVA, might be difficult to generalize. (2) We did not measure other relevant variables for the development of VILI, such as end-expiratory lung volume²⁸ and heterogeneity²⁷; however, we expect that both likely improved as increased effort usually recruits the lung²⁹ and promotes more homogeneous redistribution of Vt.²⁷; (3) Study phases lasted only 20 min, but this seemed adequate to obtain stable gas exchange and to show modifications in the respiratory pattern without an unnecessary prolongation of the study period that already lasted around 160 min per patient. (4) We studied patients at a rather late phase of recovery from severe ARDS and 6 (75%) of them were tracheostomized (table 1). However, in our patients, ventilation support was still elevated at the time of the study (*e.g.*, mean PEEP level was 13 cm H₂O) (Table 1). (5) Most of our results actually reflect basic physiology: for example, during exercise, a linear correlation exists between minute ventilation and oxygen consumption,³⁰ which, similar to that in our study protocol, is always

accompanied by increase of carbon dioxide burden on the lungs. Nevertheless, to date, only few studies have described in detail the respiratory physiology of spontaneously breathing patients recovering from severe ARDS on ECMO.^{11,13,14} The fact that, in our study, patients' response expected from basic physiology might be related to clinical characteristics of our patients' population (*e.g.*, patients studied at a rather late phase of recovery from severe ARDS, see point 5) and more research should be performed on respiratory control by ECMO at an earlier stage of severe ARDS. (6) Our study interventions were not blinded to experimenters. However, we do not think that blinding of interventions (*i.e.*, PSV and NAVA) was feasible as experimenters needed to change the ventilation strategy eight times in the same patient. Moreover, most of the variables reported are operator independent, such as RR, V_t, EAdi, and V_{CO₂}. Finally, we tried to strictly control all external factors that could affect respiratory drive and effort (*e.g.*, creation of calm environment, stable sedation level). In conclusion, we showed that, in spontaneously breathing ECMO patients recovering from severe ARDS undergoing both PSV and NAVA, the amount of extracorporeal carbon dioxide removal influences the respiratory drive and effort and it may be critical to limit the risk of VILI. In these patients, respiratory function and physiologic variables at different levels of extracorporeal support should be closely monitored.

Research Support

The present study was supported by departmental funding and by the Italian Ministry of Instruction, University and Research, Rome, Italy.

Competing Interests

The authors declare no competing interests.

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